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## Early detection of patient deterioration in patients with infection or sepsis

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## Chapter 7

# Heart rate variability as early warning for patient deterioration in emergency department patients with sepsis: the study protocol of the SepsiVar study.

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### PUBLISHED AS

Quinten VM, van Meurs M, Renes MH, Ligtenberg JJM, Ter Maaten JC. Protocol of the sepsivar study: a prospective observational study to determine whether continuous heart rate variability measurement during the first 48 hours of hospitalisation provides an early warning for deterioration in patients presenting with infection or sepsis to the emergency department of a Dutch academic teaching hospital. *BMJ Open* 2017; 7: e018259.

## Abstract

### INTRODUCTION

One in five patients with sepsis deteriorates within 48 hours after hospital admission. Regrettably, a clear tool for the early detection of deterioration is still lacking. The SepsiVar study aims to determine whether continuous heart rate variability (HRV) measurement can provide an early warning for deterioration in patients presenting with suspected infection or sepsis to the emergency department (ED).

### METHODS AND ANALYSIS

The protocol of a prospective observational study in the ED. We will include 171 adult medical patients presenting with suspected infection or sepsis and at least two systemic inflammatory response syndrome criteria. Patients with known pregnancy, cardiac transplantation or not admitted to our hospital are excluded. High sample frequency ECG signals (500 Hz), respiratory rate, blood pressure and peripheral oxygen saturation will be recorded continuously during the first 48 hours of hospitalization using a bedside patient monitor (Philips IntelliVue MP70). Primary endpoint is patient deterioration, defined as the development of organ dysfunction, unplanned intensive care unit admission or in-hospital mortality. The ECG data will be used for off-line HRV analysis. We will compare the HRV between two groups (deterioration/no deterioration) and analyze whether HRV provides an early warning for deterioration. Furthermore, we will create a multivariate predictive model for deterioration based on heart rate, respiratory rate and HRV. As planned secondary analyses, we (1) perform a subgroup analysis for patients with pneumosepsis and urosepsis and (2) determine whether HRV using lower sample frequencies (1 Hz or less) suffices to predict deterioration.

### ETHICS AND DISSEMINATION

The Institutional Review Board of the University Medical Center Groningen granted a waiver for the study (METc 2015/164). Results will be disseminated through international peer-reviewed publications and conference presentations. A lay summary of the results will be provided to the study participants.

### TRIAL REGISTRATION NUMBER

NTR6168; Pre-results.

## Introduction

Despite the adoption of Surviving Sepsis Campaign (SSC) guidelines, early goal-directed therapy and decades of fundamental, translational and clinical research, sepsis-related morbidity and mortality remain unacceptably high<sup>1,2</sup>. Previous studies have shown that one in five patients presenting to the emergency department (ED) with infection or sepsis, deteriorate; most frequently within 48 hours after hospital admission<sup>3,4</sup>. It remains unclear how early signs of patient deterioration and the response to treatment can be monitored in sepsis<sup>2,5</sup>. The most recent SSC guidelines suggest that a thorough re-evaluation of available physiological variables, including routinely measured vital signs, may describe the patient's clinical state and the response to treatment<sup>2</sup>.

Traditionally, the diagnosis and monitoring of sepsis are based on infrequently measured discrete absolute values of vital signs, non-specific symptoms and scoring systems. In clinical practice, the crossing of certain thresholds of these vital signs are used to confirm the diagnosis and to monitor the response to treatment. These thresholds are derived from epidemiological research. However, because of the heterogeneous patient population and the unpredictability of an individual's response to treatment, thresholds for the '*average*' patient may not apply to or be beneficial for individual patients<sup>6</sup>.

Although vital signs of patients are continuously measured in the ED or intensive care unit (ICU), most of the measured data are discarded by only using discrete absolute values<sup>6,7</sup>. Monitoring changes in vital signs over time, called variability analysis, provides an additional dimension to the data being measured and may provide information about response to treatment or early signs of patient deterioration<sup>7,8</sup>.

Like many other biological systems, the host response to infection is a complex non-linear system. Complex non-linear systems are composed of a virtually infinite number of interconnected variables, which are constantly changing. Complex systems have emergent properties that none of the individual parts have and that disappear on decomposition of the system into smaller parts. Small perturbations of individual variables in the system may be magnified or dampened depending on the state of the system, which may cause unpredictably large changes. The properties of a complex system help explain why chaotic dynamics may lead to unexpected rapid deterioration or clinical improvement without identifiable cause<sup>6</sup>. Changes of individual variables over time are called variability. Despite large degrees of variability of individual variables, the system as a whole will naturally settle in a remarkably small number of stable states. By using continuous variability analysis over time, it is theoretically possible to track the '*state of the system*' over time. Furthermore, variability analysis could be used to determine prognosis and response to treatment of individual patients contrary to traditional epidemiological thresholds<sup>7</sup>. Therefore, continuous variability analysis has the potential to determine whether an individual patient is progressing towards a state of health or towards deterioration.

Many types of vital signs can be analyzed using variability analysis, however, heart rate variability (HRV) is the most studied. HRV can be measured readily, easily, non-invasively and the most accurately<sup>9</sup>. Although a couple of studies have been performed on HRV in adults with sepsis, variability analysis is most studied and successfully applied in neonates<sup>6</sup>. The leading bedside clinical application of HRV has been studied in neonates by Moorman *et al*<sup>10</sup>. They

created a composite measurement of HRV that predicts an increased likelihood of deterioration in the subsequent 24 hours<sup>6</sup>. In the adult population, HRV has mostly been studied in small pilot studies and studies in ICU patients with sepsis and septic shock<sup>6</sup>. Reduced HRV has been associated with the diagnosis of sepsis, impending shock and patient deterioration<sup>6</sup>. In a small study, Barnaby *et al*, found a HRV threshold discriminating between deterioration and no deterioration<sup>11</sup>. A study by Pontet *et al* in ICU patients suggests that a reduced HRV at ICU admission may be useful in identifying septic patients at risk for multiple organ failure<sup>12</sup>. The question remains whether a reduction in HRV is also present in patients presenting to the ED with infection or sepsis, since these patients appear to be generally less severely ill than ICU patients, and whether reduced HRV can be used as an early warning signal for impending patient deterioration in the ED population.

## OBJECTIVES

The primary objective of the SepsiVar study is to determine whether continuous HRV measurement in patients presenting to the ED with suspected infection or sepsis during their first 48 hours of hospitalization can provide an early warning signal for patient deterioration. Furthermore, we plan a secondary analysis, to determine whether variability analysis of the heart rate using a lower sample frequency (1 Hz or less) would also be sufficient to predict patient deterioration.

## Methods and analysis

### STUDY DESIGN AND SETTING

The SepsiVar study is a prospective observational study. The study will be conducted in the ED of the University Medical Center Groningen in the Netherlands, a tertiary care teaching hospital with over 34 000 ED visits annually. The SepsiVar study is part of the research line on sepsis and infection in our department. One of the goals of this research line is to create a model for patient deterioration and response to treatment in ED patients with suspected infection or sepsis. To create this model, we study various predictive variables, like clinical scoring systems, biomarker levels and vital signs<sup>8,13</sup>. We have a special interest in patients with infection and sepsis without organ failure, since many of these patients deteriorate and they may benefit the most from early intervention<sup>3,4,14</sup>.

### STUDY POPULATION

Consecutive medical patients visiting the ED with fever and/or suspected infection or sepsis, will be screened for eligibility to be included in the study. The inclusion criteria are: (1) age of 18 years or older, (2) suspected infection or suspected sepsis, (3) two or more systemic inflammatory response syndrome criteria as defined by the International Sepsis Definitions Conference and (4) able to provide written informed consent<sup>15</sup>. Patients are excluded from the study in case of: (1) known pregnancy, (2) when the patient is not admitted to the hospital from the ED or is transferred to a location outside our hospital (e.g., another hospital, nursing home, long-term care facility, etc) or (3) the patient had a cardiac transplantation. Patients with a cardiac transplantation are excluded since it is known that they have a highly

reduced HRV<sup>16</sup>. The original design and ethics approval for this study originate from before the introduction of the Sepsis-3 definitions; therefore, the inclusion criteria are based on the Sepsis-2 definitions<sup>15,17</sup>. We chose not to adjust the inclusion criteria to the Sepsis-3 definitions, since patients meeting the Sepsis-3 criteria have signs of organ failure by definition<sup>17</sup>. However, in terms of the new Sepsis-3 definitions, we are especially interested in the patients who present in the ED with infection and deteriorate to sepsis within 48 hours after hospital admission. This group of patients has the highest potential to benefit from early intervention when (early) signs of organ failure are detected.

## ENDPOINT AND DEFINITIONS

The primary endpoint for this study is patient deterioration. We define patient deterioration as the development of organ dysfunction, unplanned ICU admission or in-hospital mortality. For organ dysfunction, we distinguish between acute kidney injury (AKI), liver failure and respiratory failure, as defined below. For AKI, the Kidney Disease Improving Global Outcomes guideline criteria will be used<sup>18</sup>. Liver failure is defined as total bilirubin level  $>34.2 \mu\text{mol/L}$  ( $2.0 \text{ mg/dL}$ ) and either alkaline phosphatase or a transaminase level greater than two times normal<sup>19</sup>. Respiratory failure is defined as the need for mechanical ventilation or either hypoxemia ( $\text{PaO}_2 < 8.0 \text{ kPa}$ ) or hypercapnia ( $\text{PaCO}_2 > 6.5 \text{ kPa}$ ) in the arterial blood gas analysis or a peripheral oxygen saturation  $<90\%$  when breathing ambient air or  $<95\%$  with at least  $2 \text{ L/min}$  of oxygen supplementation<sup>20</sup>. Unplanned ICU admission was defined as a transfer to the ICU of a patient from a general ward during the patient's stay in the hospital for any reason. In-hospital mortality is defined as all-cause mortality during the patient's stay in the hospital.

## DATA COLLECTION

Eligible patients visiting our ED between 8:00 and 23:00 will be recruited for the study by a trained member of our research staff. After consent from the patient, high sample rate vital signs will be recorded (Table 1). The data collected by the research staff, furthermore, include sociodemographic information, patient history, treatment parameters, results from routine blood analysis and follow-up during the patient's stay in the hospital. The patient's electronic medical records will be used as a source for patient characteristics and for patient follow-up.

The high sample rate vital signs (Table 1) of participants in the study are measured using a mobile bedside patient monitor (Philips IntelliVue MP70 System with Multi-Measurement Module; Philips, Eindhoven, The Netherlands) during the first 48 hours of hospitalization. Patients transferred from the ED to the nursing wards are normally not continuously monitored on the wards; therefore, the mobile patient monitor is transferred with the patient to the ward. All alarms on the mobile patient monitor are deactivated and the option to set any alarms has been disabled. The deactivated alarms minimize the potential influence of the monitoring on the care process on the wards. Furthermore, sounding alarms may worry the patient. The data on the screen of the monitor are available to the ward staff, as this was an essential requirement for their cooperation.

Patients transferred to the ICU are continuously monitored using the stationary bedside monitors in the ICU (of the same model as the mobile bedside monitor). Since these monitors are essential for patient monitoring and care in the ICU, no changes are made to the monitor's settings; alarms can be configured or enabled at the discretion of the ICU staff. Although

**TABLE 1. Measured vital parameters and sample frequencies**

Wave forms	Sample frequency*
ECG (using EASI™ lead placement)	
Lead I	500 Hz
Lead II	500 Hz
Lead V5	500 Hz
Respiratory wave form	125 Hz
Plethysmogram wave form	125 Hz
<b>Numeric values</b>	
ECG heart rate	1 Hz
Respiratory rate (ECG impedance)	1 Hz
Peripheral oxygen saturation	1 Hz
Peripheral flow index	1 Hz
Plethysmogram pulse rate	1 Hz
Non-invasive blood pressure	Every 4 hours

\* The samples are recorded at the maximum frequency supported by the Philips Data Export Protocol for the Philips Intellivue MP70 patient monitor<sup>20</sup>.

high sample rate vital signs are routinely measured in the ICU, most of the data are not stored and thus discarded<sup>6</sup>. Therefore, both on the wards and on the ICU, the patient monitor is connected to a laptop containing custom-made software to record and store this data. The software uses the Philips IntelliVue Data Export Interface Protocol to record the vital sign data of the patient monitor with the highest supported sample frequency (Table 1) and it stores the raw data into a database<sup>21</sup>. The raw data in this database will be used as a source for the off-line analysis of HRV.

## DATA ANALYSIS PLAN

The raw ECG data stored in the database needs to be preprocessed before it can be used for the off-line analysis of HRV. Preprocessing consist of several steps. First, baseline wander, power line and movement artifacts as well as other noise will be filtered out of the raw signal. Second, non-sinus rhythm ectopic beats will be detected and corrected for using an interpolation algorithm, since these beats cause an artificially high HRV<sup>22</sup>. Third, the R-peaks will be detected in the resulting signal. The result of the preprocessing are the time periods between two successive R-peaks, that is, the R-R intervals.

After preprocessing, the R-R interval data will be used for HRV analysis in the time domain and in the frequency domain (the technical terms of HRV analysis are explained in Appendix A on page 125)<sup>7,16</sup>. The time domain consists of a statistical evaluation of the R-R interval data. A reduced HRV measured in the time domain has been associated with poor prognosis and/or increased mortality for other diseases (described above)<sup>7</sup>. We will calculate the SD of N-N intervals (Appendix A on page 125) for the time domain, which reflects the variability caused by all cyclic components in the period of the recording<sup>16</sup>.

The frequency domain will be analyzed by determining the power in predefined frequency bands: high frequency (HF, 0.15–0.4 Hz), low frequency (LF, 0.04–0.15 Hz) and very low frequency (0.003–0.04 Hz) band. The power in the HF band is mainly influenced by vagal activity. The LF band indicates sympathetic activity, although some studies suggest that vagal activity plays a role as well<sup>22,23</sup>.

The preprocessing of the raw data and the analysis of the HRV will be performed by an automated algorithm implemented in MATLAB (The MathWorks, Natick, Massachusetts, USA), to prevent a subjective bias in the HRV analysis. The algorithm will be developed and the HRV analysis will be performed by a member of our research staff who is blinded to the clinical outcomes of the patients. Before analyzing our own data using the algorithm, the algorithm's accuracy will be tested using the MIT-BIH arrhythmia database<sup>24</sup>. The MIT-BIH database contains 48 ECG recordings including annotations of R-peaks, noise and ectopic beats and can therefore be used to validate our algorithm.

We will compare the HRV measurements between two groups (deterioration/no deterioration) using a t-test after logarithmic transformation of the data, since the data will likely have a  $\chi^2$  distribution. We will perform a windowed, time-locked to onset of deterioration, logistic regression analysis to look at which moment in time there is a significant difference in HRV between the groups, that is, an early warning of patient deterioration. Furthermore, we will create an initial predictive model for deterioration based on heart rate and respiratory rate, using multivariate logistic regression. By forward variable selection, we will extend this model with the HRV measurements to analyze whether these measurements improve the predictive accuracy of the model. The regression model is considered a hypothesis-generating analysis to analyze the added value of HRV over traditionally recorded vital signs for a future larger follow-up study.

The focus of sepsis may have an influence on the HRV measurements. Therefore, we plan a secondary analysis in which we will perform a subgroup analysis for patients with pneumosepsis and urosepsis for the HRV measurements mentioned above.

To determine whether heart rate measurements with a sample rate of 1 Hz or less also discriminate the two groups (deterioration/no deterioration), we plan another secondary analysis depending on the discriminating power found by the primary analysis. These lower sample rates would enable the use of wearable or low-cost devices to monitor patient deterioration and would dramatically reduce the amount of data that need to be stored, processed and analyzed.

HRV is mostly and preferably measured under controlled circumstances<sup>16</sup>. However, we measure HRV in patients who are potentially mobile in various hospital environments (ED, ICU and nursing wards). To determine the possible effects of interference or artifacts and the quality of our measurements, we plan an interim analysis of the data after inclusion of the first 25 patients.

## **SAMPLE SIZE**

This study's sample size was calculated using data from a pilot study in our department and information available in literature<sup>8</sup>. In the pilot study, overall rate of patient deterioration during hospitalization was 36%<sup>8</sup>. Studies using HRV to predict mortality, sepsis severity and impending septic shock have reported highly variable effect sizes for the various HRV measurements<sup>12,25-29</sup>. Since these measurements all provide their own distinct information, it is difficult to designate one of them as the most important and to base the estimated effect size on that measurement<sup>7</sup>. The majority of effect sizes (Cohen's d) reported are well over d=0.6, therefore, we chose this value as a conservative estimate for effect size. We chose a conservative estimate to prevent overestimation of the expected difference between the deterioration/ no



**TABLE 2. Calculation of the study's required sample size**

<b>Sample size calculation</b>	
Test: 2-tailed t-test difference between two independent groups	
Power	80%
$\alpha$	0.05
Estimated effect size d	0.6
Estimate group allocation ratio N2/N1 (36% deterioration)	0.36
Calculated sample size	114
<b>Corrections</b>	
Estimated loss to follow-up	+20%
Estimated dysrhythmia	+10%
Subgroup analysis for pneumosepsis and urosepsis (70% of patients)	+30%
Required sample size	171

deterioration groups. Using the information described above, we calculated the required sample size for the study using G\*Power: Statistical Power Analyses for Windows<sup>30</sup>. The power calculation resulted in a minimum sample size of 114 patients (Table 2).

To ensure sufficient power of the study results, we performed a number of corrections on the calculated sample size. First, we estimated that 20% of the patients who participate in the study may drop out of the study for various reasons, for example, early discharge, patient discomfort (continuous measurement), development of delirium and so on. Second, it is important that HRV calculations are performed on subsequent beats of a sinusoidal rhythm, as ectopic beats and arrhythmic events affect the outcomes of these calculations<sup>16</sup>. Therefore, we corrected for patients with dysrhythmia. The incidence of dysrhythmias in patients with sepsis is approximately: 8% in patients with sepsis, 10% in severe sepsis and 23% in septic shock patients<sup>19</sup>. The ratio between sepsis, severe sepsis and septic shock in our department is approximately 6:3:1 based on data from our pilot study and another study in our department<sup>8,13</sup>. We calculated, using a weighted average and this ratio that approximately 10% of the patients in our population will have dysrhythmia. Third, we corrected for the planned secondary analysis in the subgroups with pneumosepsis and urosepsis. Together, these two sources of sepsis account for approximately 70% of all patients presenting with sepsis to our ED. Therefore, we corrected the sample size with 30% to account for other sources of sepsis. After these three corrections, the required sample size for the study is 171 patients (Table 2).

## **DURATION AND CURRENT STATUS OF THE STUDY**

The study was prospectively registered in The Netherlands National Trial Register on 4 January 2017 under number NTR6168. Recruitment of patients is ongoing and the first patient was included on 16 January 2017. At the time of writing (June 2017), 34 patients have been included in the study. It is expected that the required sample size of 171 patients will be reached by the first quarter of 2018.

## Ethics and dissemination

### ETHICAL ASPECTS AND INFORMED CONSENT

This study will be carried out in accordance to the Declaration of Helsinki, the Dutch Agreement on Medical Treatment Act and the Dutch Personal Data Protection Act. The Institutional Review Board of the University Medical Center Groningen ruled that the Dutch Medical Research Involving Human Subjects Act is not applicable for this study and granted a waiver.

Eligible patients visiting the ED will be asked to participate in the study by a member of our research staff. On agreement to participate, the patient will be asked to provide written informed consent. Participants are informed that they can withdraw their informed consent at any moment without the need to provide a reason. In case a participant withdraws informed consent, data collection will be ended immediately and the data will be discarded. Participants are also informed that they can end their participation in the study at any moment, for example, when the patient experiences too much discomfort from the monitor cables or ECG electrodes. However, in the latter case, the data collected until that point will be used in the final analysis.

Additional risks for patients caused by participation in the study are negligible. All participants will receive standard care according to the hospital's protocols and the attending physician's discretion. Participation in the study does not involve any alterations in treatment protocol<sup>8</sup>.

### PROTOCOL COMPLIANCE

The study will be performed in accordance to the study protocol reviewed by the Institutional Review Board. Any changes to the protocol first need approval from the Review Board before they can be put into practice, except if following the original protocol presents an immediate risk to the patient. Any deviations from the protocol will be recorded and when required reported to the Institutional Review Board.

### DISSEMINATION

On conclusion of the study, the results will be disseminated via international peer-reviewed journals and conferences. We plan to disseminate the results of the planned secondary analysis with lower sample rate (<1 Hz) vital signs in a separate manuscript. However, we will ensure that the manuscript will contain the proper cross-references and preferably submit it to the same journal. A lay summary of the results will be provided to the study participants.

## Potential impact and future plans

The SepsisVital study will be, to the best of our knowledge, the largest study of its kind that prospectively records high sample frequency vital signs with the objective to develop an early warning signal for patient deterioration using HRV in patients presenting with suspected infection or sepsis to the ED. Furthermore, it is the first study that continuously records high sample frequency ECG signals for 48 hours and also other vital signs like respiratory rate,

oxygen saturation and plethysmogram (Table 1). Although our primary focus lies on the variability analysis using the ECG signal, the recorded data of the other vital signs may be used to optimize the model for patient deterioration. The study has, therefore, the potential to discover a new tool for patient deterioration in this ED patient population.

The bedside patient monitors used in clinical practice today, require lots of wires between the monitor and the patient's body. These monitors, therefore, restrict patients in their movements and mobility. The cables and electrodes may, furthermore, cause discomfort to the patient. Therefore, we plan to investigate the use of wearable devices for the monitoring of patients in the future. Wearable devices may improve the ease of measurement and patient comfort.

If the results of the SepsiVar study can reliably differentiate between patients who deteriorate and those who do not deteriorate based on HRV and provide early warning of deterioration, we plan to implement continuous measurement of ECG signals with (near) real-time analysis of HRV in our ED. This early warning system using continuous variability analysis can potentially be used to monitor response to treatment in sepsis and to guide treatment. Furthermore, we plan to develop a self-learning computer-guided early warning model for patient deterioration by integrating various variability measures and biomarker values using machine learning technology. This model may provide a tool to improve care for and outcomes of patients with infection and sepsis in the ED.

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